Remarks

Currently Claims 5-6, 14-15, and 19-37 are pending. Claim 21 is amended to remove parenthetical expressions. New claims 30-37 are added. Support for these claims can be found throughout Applicants' original specification, including at page 8, lines 14-20; page 11, lines 14-17; page 13, lines 16-32; page 14, line 32 through page 15, line 7; and original claims 1-18. No new matter is added. Entry of the foregoing amendments is respectfully requested.

Applicants wish to clarify that the instant invention relates to EP4 receptor ligands.

Affirmation of Election

Claims 5-6, 14-15 and 19-29 are subject to an election of species requirement.

Applicants hereby affirm the provisional election of compound species (IF) as the EP4 receptor ligand and COX-2 inhibitors as the second therapeutic agent. This election is made without traverse with the understanding that upon the finding of an allowable species, examination will continue with the non-elected species until all species have been examined or a non-allowable species is found pursuant to MPEP 809.04.

Applicants respectfully submit that new claims 30-37 are ripe for consideration with the elected species inasmuch as the new claims recite the elected species, compositions containing the same, methods of using the same and a process for the preparation of the same.

Claim Objections Overcome

Claim 21 currently stands objected to for reciting parenthetical expression. Applicants respectfully submit that the foregoing amendment to claim 21

overcomes this rejection. Applicants further respectfully submit that the amendment does not narrow the scope of the claims.

Section 112, First Paragraph Rejection Overcome

Claims 5-6, 14-15 and 19-29 currently stand rejected under 35 U.S.C. §112, first paragraph, the Office Action stating that the specification, while enabling for EP4 ligands represented on pages 3-8 of the specification, does not reasonably provide enablement for any and all EP4 ligands. Applicants respectfully traverse this rejection.

Applicants submit that the Office Action does not meet the burden of establishing a *prima facie* case of lack of enablement. The Office Action states that Applicants have failed to set forth the criteria defining an EP4 ligand and have failed to provide information allowing the skilled artisan to ascertain these compounds without undue experimentation. The Examiner also states that given the structural diversity of EP4 ligands the skilled artisan would not be able to ascertain which compounds would be suitable for the practice of in this invention. Applicants respectfully submit that the instant invention does not attempt to define a subset of EP4 ligands, but rather is directed toward all EP4 receptor ligands. Accordingly, Applicants are not required to define *criteria* for selecting particular EP4 ligands for use in the present invention. Furthermore, the term "EP4 ligand" was, as of Applicants' priority date, a recognized term of art (*see*, Coleman, et al., *Advances in Prostaglandin, Thromboxane, and Leukotriene Research* **23**:241 (1995) (copy attached)), which Applicants have employed in a manner consistent with its generally accepted meaning. The term is understood in the art to define a recognized class of compounds which bind to the EP4 receptor.

Methods for identifying compounds which are EP4 ligands were known in the art as of Applicants priority date, as well. *See*, Marshall et al., *British Journal of Pharmacology* **121**:1673 (1997) (copy attached). In addition, Applicants have described an assay method which for evaluating a particular compound

for EP4 receptor binding ability. See pages 9-10. Given the state of the art as of Applicants' priority date regarding EP4 receptor ligands and methods for identifying the same, it is respectfully submitted that it is appropriate to omit such disclosure from the instant patent application. *See*, MPEP 2164.01 "A patent need not teach, and preferably omits, what is well known in the art," citing *In re Buchner*, 18 USPQ2d 1331 (Fed. Cir. 1991).

The Examiner further states that the field of art is unpredictable and that the genus of EP4 ligands is vast and would necessitate an exhaustive search. Applicants respectfully note that the extent of the search required is not an appropriate consideration under either the standard for enablement or the *Wands* factors.

Applicants further submit that under both the holding and recited factors of *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the instantly pending claims are fully enabled. In *Wands*, the Federal Circuit found that the claims were properly enabled even where one of ordinary skill in the art would have to engage in production and screening of numerous monoclonal antibodies to practice the invention.

Just as in *Wands*, the present application discloses a method for producing the product (here EP4 ligands; in *Wands*, monoclonal antibodies) and working examples. The present specification discloses EP4 receptor ligands by chemical name, structure and function, including the identification of various patents which disclose EP4 ligands and a preferred EP4 ligand (compound IF). *See*, pages 2 to 8. An example of the preparation of the compound of formula IF is disclosed at pages 15-19.

Applicants further submit that just as Wands disclosed a screening assay, so does the present specification. The screening method for determining if compounds are EP4 receptor ligands is disclosed at pages 8-10 of the specification. Just as the *Wands* court recognized that the method for screening monoclonal antibodies was well known prior to the Applicants filing

date, the methods for screening for EP4 receptor ligands were well known prior to Applicants' priority date. *See,* the Marshall article dated 1997.

Furthermore, the level of predictability in the Wands invention and the level of predictability in the present invention are relatively the same.

Accordingly, applying the holding and factors of *Wands* to the present case, the Office Action fails to establish a *prima facie* case of lack of enablement and withdrawal of this rejection is respectfully requested.

Section 103 Rejections Overcome

Claims 22-24 and 27-29 currently stand rejected under 35 U.S.C. §103(a) as being unpatentable over Foord '307 in view of Katzung. The Office Action acknowledges that Foord '307 does not teach the combination of an EP4 ligand and a COX-2 inhibitor, but concludes that this combination would have been obvious at the time of the invention. Applicants respectfully traverse this rejection.

Applicants have found that the combination of an EP4 ligand and a COX-2 inhibitor possesses unexpectedly superior properties useful for the treatment of pain. In particular, Applicants have found that the instantly claimed combination provides synergistic effects in a model of inflammatory pain. Filed concurrently herewith is the Rule 132 Declaration of Nicholas M. Clayton attesting to the experiments conducted and the results obtained which show that in both Experiments 1 and 2, the EP4 ligand (0.1 or 0.03 mg/kg p.o.) and the COX-2 inhibitor (0.3 or 0.1 mg/kg p.o.) each alone had no significant effect on the hypersensitivity to pain, but the combination of EP4 ligand and COX-2 inhibitor produced a synergistic effect on the percent inhibition of hypersensitivity. Applicants respectfully submit that the foregoing remarks and the accompanying Rule 132 Declaration of Nicholas M. Clayton overcome the instant rejection and respectfully request withdrawal thereof.

Applicants respectfully submit that the instant application is in condition for allowance, which action is respectfully requested. The Examiner is invited to contact the undersigned at (919) 483-8222, to discuss this case further if desired.

Respectfully submitted,

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